Exhibit 3

Pharmaceutical Sciences

1990

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Remington's Pharmaceutical Sciences . . . *a treatise on the theory and practice of the pharmaceutical sciences, with essential information about pharmaceutical and medicinal agents; also a guide to the professional responsibilities of the pharmacist as the drug-information specialist of the health team . . . A textbook and reference work for pharmacists, physicians and other practitioners of the pharmaceutical and medical sciences.*

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tion of the compound is followed by a dramatic rise in blood pressure due to the release of excessive quantities of epinephrine and norepinephrine from the neoplasm. It has a few other minor diagnostic applications. Since the "flare" that results from intracutaneous injection of this agent is mediated by an axon reflex, this approach has been used as a test for the integrity of sensory nerves; the wheal that results has been used as a test for circulatory competency.

Adverse reactions are observed even after small doses, such as employed in gastric analysis (0.01 mg/kg subcutaneously). These include flushing, dizziness, headache, bronchial constriction, dyspnea, visual disturbances, faintness, syncope, urticaria, asthma, marked hypertension or hypotension, palpitation, tachycardia, nervousness, abdominal cramps, diarrhea, vomiting, metallic taste, allergic manifestations or collapse with convulsions. The hypotension usually is postural and requires no treatment other than assuming a recumbent position. If treatment is required, epinephrine (0.3 mg SC) is an effective physiological antagonist.

Dose—*Diagnostic, gastric test, subcutaneous*, 27.5 μg (equivalent to 10 μg of histamine)/kg. *Usual range of dose*, 10 to 40 μg/kg. *Pheochromocytoma test, intravenous*, 10 μg and monitor blood pressure and pulse every 30 sec; if no response within 5 min, repeat with 50 μg and monitor blood pressure and pulse as above for 15 min.

Dosage Forms—Injection: 0.55, and 2.75 mg/mL.

Pentagastrin—page 1281.

Antihistamines

All clinically available antihistamines antagonize histamine to approximately the same extent, regardless of their chemical class (ethanolamines, ethylenediamines, alkylamines, phenothiazines or piperidines). Except for phenindamine, a piperidine, they all induce some sedation and anticholinergic activity. Phenindamine may induce some stimulation. Only the ethanolamines and phenothiazines possess antiemetic properties. The clinical and pharmacological differences, therefore, are related chiefly to variations in adverse effects and to nonhistamine antagonizing actions, such as their atropine-like effects, central nervous system effects (depression, stimulation, antiemetic, antitremor and motion sickness) and local anesthetic properties. A knowledge of these factors is essential for proper drug selection.

All presently available antihistamines (H_1-receptor antagonists) act by competitively antagonizing the effects of histamine at receptor sites; they do not block the release of histamine and, hence, offer only palliative relief of allergic symptoms. After oral administration, effects are apparent within 15 to 30 min, are maximal within 1 hr and persist for 4 to 6 hr. The liver is the principal site of metabolism; the agents are excreted in urine as unidentified metabolites.

Clinically, indications for the use of the various antihistaminic drugs vary considerably. The majority of these agents are *effective* in *perennial* and *seasonal allergic rhinitis, vasomotor rhinitis, allergic conjunctivitis, urticaria and angioedema, allergic reactions to blood and plasma, dermographism* and as adjuncts to conventional therapy in *anaphylactic reactions*. A few antihistamines probably are effective in mild, local *allergic reactions to insect bites, physical allergy* and minor *drug* and *serum* reactions characterized by *pruritus*. Selected antihistamines (eg, diphenhydramine hydrochloride) reduce rigidity and tremors in *paralysis agitans* (Parkinson's disease) and in *drug-induced extrapyramidal symptoms*. Some antihistamines (eg, buclizine, cyclizine, dimenhydrinate, diphenhydramine, meclizine and others) also are effective in the *active and prophylactic management of motion sickness*. The more sedative agents (eg, diphenhydramine, doxylamine, promethazine and others) sometimes are used as substitutes for barbiturates in *insomnia* and *insomnia* predominant in certain medical disorders. Certain antihistamines, such as chlorpheniramine, doxylamine succinate and pyrilamine maleate, are used in proprietary medication advertised as daytime sedatives and sleep aids. Methapyrilene, formerly used in virtually all nonprescription sleep aids in the US, was removed from these products in 1979 because of its possible carcinogenic properties.

The phenothiazine antihistamines possess other useful clinical properties not shared by conventional antihistamines. For example, promethazine hydrochloride is useful for *preoperative, postoperative* and *obstetric sedation*; prevention and control of *nausea* and *vomiting* associated with certain types of anesthesia and surgery and as *adjunctive therapy* to meperidine or other analgesics for the *control of postoperative pain*.

The usefulness of antihistamines in various other clinical conditions, such as bronchial asthma, atopic dermatitis, neurodermatitis, allergic eczema, various contact and chemotoxic dermatitides, generalized pruritus, and for cardiac arrhythmias, spasmolysis in gastrointestinal allergies, prophylaxis of drug reactions, etc, must await further clinical investigation before a final assessment can be made.

It is agreed generally that *most* antihistamines are *ineffective* in migraine and histamine headache, prevention or reduction of the sequelae of pain, edema and hemorrhage in oral surgery, potentiation of narcotic analgesic drugs, as antiemetics in postoperative patients, as antitussives, or for treatment of nocturnal leg cramps, leg cramps of pregnancy and functional dysmenorrhea.

The most common side effect of antihistamines is sedation, evidenced principally by drowsiness, plus a diminished alertness and ability to concentrate. Less-common effects—unless large doses are used—include dryness of the mouth, blurred vision, vertigo and gastrointestinal distress (see also above). The sedative effect may be so intense as to impair driving ability and performance of duties requiring mental alertness. Other side effects elicited by these drugs include nausea, headache and restiveness. Dermatologic complications and skin eruptions have followed local application or oral administration of antihistamines. In a few individuals, certain antihistamines produce signs of central excitation such as insomnia and nervousness. Since the depressant effects of alcoholic beverages and other drugs that depress the central nervous system (tranquilizers, hypnotics, sedatives, antianxiety agents, depressants, analgesics, etc) are increased by antihistamines, the physician may forbid concurrent use or modify the conditions of such use. Patients being treated with MAO inhibitors, or who have been treated with such drugs within the preceding 2 weeks, should not be given antihistamines.

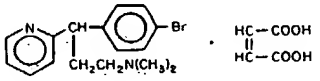
Because of their drying effect on mucous membranes, antihistamines may exacerbate wheezing and therefore should not be used during an asthmatic attack. Because of the anticholinergic action of antihistamines, their use in the following diseases may be contraindicated or subject to great caution: narrow-angle glaucoma, prostatic hypertrophy, stenosing peptic ulcer, pyloroduodenal obstruction, bladder-neck obstruction, increased intraocular pressure, history of bronchial asthma, hyperthyroidism, cardiovascular disease or hypertension. Antihistamines should not be given to premature or newborn infants, and may be denied by the physician for patients breast-feeding infants.

These brief observations call attention to the enormous number of clinical conditions for which antihistaminic drugs have been suggested. They also point up the fact that these drugs vary from *effective* to *ineffective* in these conditions. When considering the multiplicity of available antihistamines, their numerous untoward reactions and their propensity to induce sedation of variable intensity, one can appreciate the complex therapeutic problem that confronts the thoughtful physician in the selection of an antihistamine for

a particular patient with a histamine-related clinical condition.

Brompheniramine Maleate

2-Pyridinepropanamine, γ-(4-bromophenyl)-*N*,*N*-dimethyl-, (*Z*)-butenedioate (1:1); Dimetane (*Robins*); Diamine (*Major*); (*Various Mfrs*)



2-[*p*-Bromo-α-[2-(dimethylamino)ethyl]benzyl]pyridine maleate (1:1) [980-71-2] $C_{16}H_{19}BrN_2.C_4H_4O_4$ (435.32).

Preparation—α-(*p*-Bromophenyl)-2-pyridineacetonitrile is converted to its sodium derivative with sodium amide and condensed with 2-chloro-*N*,*N*-dimethylethylamine. The resulting nitrile is hydrolyzed to the corresponding acid, which is decarboxylated by treatment with H_2SO_4. The base, obtained on alkalinization, is solvent-extracted and reacted with maleic acid.

Description—White, odorless, crystalline powder; melts 130 and 135°; pH (1 in 100 solution) 4.0 and 5.0.

Solubility—1 g in 5 mL water, 15 mL alcohol or 15 mL chloroform; slightly soluble in ether or benzene.

Uses—The bromine analog of chlorpheniramine; an antihistamine with anticholinergic (drying) and sedative side effects. It is *probably effective* for temporary relief of hay fever and upper respiratory allergy symptoms, such as itchy, watery eyes, sneezing, itching nose or throat and for amelioration and prevention of allergic reactions to blood or plasma in patients with a known history of such reactions. It appears to be well-absorbed after oral administration; peak serum concentrations of 7.7 and 15.7 ng/mL occur within 2 to 5 hr after a dose of 0.13 mg/kg; the antihistaminic effect appears maximal within 3 to 9 hr and antipruritic effect maximal within 9 to 12 hr. See also the general statement.

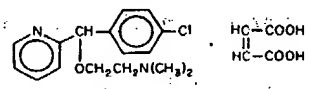
Dose—*Usual, adult, oral,* 4 mg every 4 to 6 hr; extended-release tablets, 8 or 12 mg every 12 hr. Do not exceed 24 mg in 24 hr. *Parenteral, intramuscular, intravenous,* or *subcutaneous,* 10 mg 2 times a day; maximum, 40 mg. *Pediatric, children* under 5 yr, *oral,* 125 μg/kg or 3.75 mg per m^2 every 6 hr; *children* over 6 yr, *oral,* 2 to 4 mg 3 or 4 times a day or 8 to 12 mg as extended-release tablet every 12 hr; *parenteral, children* 11 yr and under, 125 μg/kg or 3.75 mg/m^2 every 6 hr; contraindicated for premature and full-term neonates.

Dosage Forms—Elixir: 2 mg/5 mL; Injection: 10 mg/mL and 100 mg/mL. Tablets: 4 mg; Extended-Release Tablets: 8 and 12 mg.

Buclizine—page 791.

Carbinoxamine Maleate

Ethanamine, 2-[(4-chlorophenyl)-2-pyridinylmethoxy]-*N*,*N*-dimethyl-, (*Z*)-2-butenedioate (1:1); Clistin (*McNeil*)



2-[*p*-Chloro-α-[2-(dimethylamino)ethoxy]benzyl]pyridine maleate (1:1) [3505-38-2] $C_{16}H_{19}ClN_2O.C_4H_4O_4$ (406.87).

Preparation—Picolinaldehyde and *p*-chlorophenylmagnesium bromide undergo a Grignard reaction to produce *p*-chloro-α-(2-pyridyl)benzyl alcohol. This is converted into its sodium alkoxide derivative with sodamide; β-Dimethylaminoethyl chloride is added to form carbinoxamine and the base converted into the maleate by reaction with maleic acid.

Description—White, odorless, crystalline powder; melts 116 to 121°; pH (1 in 100 solution) 4.6 to 5.1; pK_a 8.7.

Solubility—1 g in <1 mL water, 1.5 mL alcohol, 1.5 mL chloroform or 8300 mL ether.

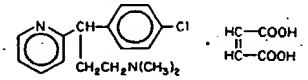
Uses—An antihistamine with anticholinergic and antiemetic activity similar to other ethanolamines. It is *probably effective* in allergic rhinitis, vasomotor rhinitis, allergic conjunctivitis, mild uncomplicated allergic skin manifestation of urticaria and angioedema. Adverse reactions are relatively mild and rarely occur; dizziness, drowsiness, nausea and dryness of the mouth have been observed. Other precautions and contraindications are the same as those for other antihistamines (see the general statement).

Dose—*Usual, adult, oral,* 4 to 8 mg 3 or 4 times a day. *Pediatric, children,* 1 to 3 yr, 2 mg 3 or 4 times a day; 3 to 6 yr, 2 to 4 mg 3 or 4 times a day; over 6 yr, 4 to 6 mg 3 or 4 times a day; contraindicated for premature and full-term neonates.

Dosage Form—Tablets: 4 mg.

Chlorpheniramine Maleate

2-Pyridinepropanamine, γ-(4-chlorophenyl)-*N*,*N*-dimethyl-, (*Z*)-2-butenedioate (1:1); Chlor-Trimeton (*Schering-Plough*); (*Various Mfrs*)



2-[*p*-Chloro-α-[2-(dimethylamino)ethyl]benzyl]pyridine maleate (1:1) [113-92-8] $C_{16}H_{19}ClN_2.C_4H_4O_4$ (390.87).

Preparation—By condensing 2-[*p*-chloro-α-(2-chloroethyl)benzyl]pyridine with dimethylamine in the presence of sodamide. Treatment of the base with an equimolar portion of maleic acid results in the formation of the maleate.

Description—White, odorless, crystalline powder; solutions are acid to litmus having a pH 4 to 5; melts 130 to 135°.

Solubility—1 g in 4 mL water, 10 mL alcohol or 10 mL chloroform; slightly soluble in ether or benzene.

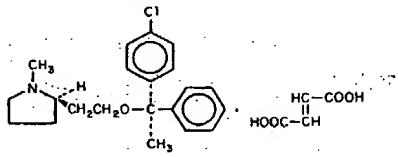
Uses—An *antihistamine* which is *probably effective* in allergic and vasomotor rhinitis, allergic conjunctivitis, mild urticaria and angioedema, allergic reactions to blood and plasma in sensitive patients, dermographism and as adjunct therapy in anaphylactic shock. It is used widely as an ingredient in proprietary antitussive formulations. It undergoes significant first-pass metabolism (40 to 55%). Peak plasma levels of 5.9 and 11 ng/mL are achieved in 2 to 6 hr. It has a low incidence of side effects, which are similar to those induced by other antihistamines. See the general statement.

Dose—*Usual, adult, oral,* 4 mg 4 to 6 times a day; extended-release capsules or tablets, 8 to 12 mg every 8 to 12 hr; *parenteral,* 5 to 20 mg as a single dose, with a maximum of 40 mg in 24 hr. *Pediatric, children* 11 yr and under, *oral,* 2 mg 3 to 6 times a day; do not exceed 12 mg in 24 hr. Extended-release forms not recommended for children under 12 yr.

Dosage Forms—Extended-Release Capsules: 6, 8 and 12 mg; Injection: 10 and 100 mg/mL; Solution: 2 mg/5 mL; Tablets: 4 mg; Chewable Tablets: 2 mg; Extended-Release Tablets: 8 and 12 mg.

Clemastine Fumarate

Pyrrolidine, 2-[2-[1-(4-chlorophenyl)-1-phenylethoxy]ethyl]-1-methyl-, [*R*-(*R**,*R**)]-, (*E*)-2-butenedioate (1:1); Tavist, Tavist 1 (*Sandoz*)



(+)-(2*R*)-2-[2-[(*R*)-*p*-Chloro-α-methyl-α-phenylbenzyl)oxy]-ethyl]-1-methylpyrrolidine fumarate (1:1) [14976-57-9] $C_{21}H_{26}ClNO.C_4H_4O_4$ (459.97).

Preparation—Various benzhydryl ethers that have histamine-inhibiting action, of which clemastine is one, may be prepared by heating a mixture of the appropriate benzhydryl bromide and *N*-methyl-2-piperidylethanol in the presence of sodium carbonate. Details of the process, as well as of an alternate synthesis, are described in British Pat 942,152 (see *CA 60*: 9250g, 1964).

Description—White to faintly yellow, crystalline powder; practically odorless; melts 176 to 181°, with decomposition.

Solubility—Very slightly soluble in water, chloroform or ether; slightly soluble in alcohol.

Uses—A long-acting *antihistamine* with anticholinergic (drying) and sedative side effects. It is indicated for relief of symptoms associated with seasonal allergic rhinitis and mild uncomplicated